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PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING TRANSMITTAL OF COPY OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (CHAPTER I OF THE PATENT COOPERATION TREATY)
(PCT Rule 44bis.1(c))

To:

BERESKIN & PARR
40 King Street West
Suite 4000
Toronto, Ontario M5H 3Y2
CANADA

Date of mailing *(day/month/year)* 02 March 2006 (02.03.2006)	
Applicant's or agent's file reference 12989-9 15289-7	**IMPORTANT NOTICE**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA2004/001503	20 August 2004 (20.08.2004)	20 August 2003 (20.08.2003)

Applicant: AMORFIX LIFE SCIENCES LTD. et al

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Athina Nickitas-Etienne

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 12989 - 9	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/CA2004/001503	International filing date *(day/month/year)* 20 August 2004 (20.08.2004)	Priority date *(day/month/year)* 20 August 2003 (20.08.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant AMORFIX LIFE SCIENCES LTD.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 21 February 2006 (21.02.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Athina Nickitas-Etienne
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PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
BERESKIN & PARR
P.O. Box 401
40 King Street West
TORONTO, Ontario
Canada, M5H 3Y2

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(date/month/year)* 24 December 2004 (24-12-2004)

Applicant's or agent's file reference	FOR FURTHER ACTION
12989-9	See paragraph 2 below

International application no	International filing date *(date/month/year)*	Priority date *(date/month/year)*
PCT/CA2004/001503	20 August 2004 (20.08.2004)	20 August 2003 (20.08.2003)

International Patent Classification (IPC) or both national classification and IPC

Primary: G01N 33/68;
Cross references: G01N 33/53, G01N 33/569.

Applicant CASHMAN, NEIL

1. This opinion contains indications relating to the following items :

[X]	Box No. I	Basis of the opinion
[X]	Box No. II	Priority
[ ]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
[X]	Box No. VI	Certain documents cited
[X]	Box No. VII	Certain defects in the international application
[X]	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**
If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/	Authorized officer
Commissioner of Patents *Canadian Patent Office* *Box PCT, Ottawa/Gatineau K1A 0C9*	David Boudreau (819) 997-2926

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CA2004/001503

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language which it was filed, unless otherwise indicated under this item.

[ ] This opinion has been established on the basis of a translation from the original language into the following language __ , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of :

a. type of material

[ ] a sequence listing

[ ] table(s) related to the sequence listing

b. format of material

[ ] in written format

[ ] in computer readable from

c. time of filing/furnishing

[ ] contained in the international application as filed.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority for the purposes of search.

3.[ ] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments :

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CA2004/001503

Box No. II Priority

1 [X] The following document has not yet been furnished :

[X] copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

[ ] translation of the earlier application whose priority has been claimed (rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2 [ ] This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purpose of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary :

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CA2004/001503

Box No. V reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

A. Novelty (N)	Claims	1-39	YES
	Claims	NA	NO
B. Inventive step (IS)	Claims	NA	YES
	Claims	1-39	NO
C. Industrial applicability (IA)	Claims	1-39	YES
	Claims	NA	NO

2. Citations and explanations :

D1: US 6406864 B2
D2: Bolton et al. (Jul 1991). *J of Virology*. **65**(7): 3667-3675.
D3: CA 2408762 A1
D4: CA 2452946 A1

Brief description of the documents:

D1 disclose an assay method involving a sample suspected of containing a protein in at least two conformations: a disease conformation and a non-disease conformation. Refer to table below for more details (Supplemental box 2).

D2 disclose a method for chemical modification of epitope (page 3671), involving DEP and succinic anhydride.

D3 disclose a conformation-dependent immunoassay method for detecting pathogenic prion proteins in a sample of a body fluid, containing both the pathological PrP protein conformation (PrPsc) and the non-pathological conformation PrPc.

D4 disclose a kit for the detection of infectious prions comprising a detecting agent. (Note that D4 was published prior to the international filing date but later than the priority date claimed.)

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Refer to Supplemental box 1

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CA2004/001503

Box No. VI **Certain documents cited**

1. Certain published documents (Rules 43*bis*.1 and 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
Soto C. Diagnosing prion diseases: needs, challenges and hopes Nature Rev Microbiol 2(10): 809-819	October 2004		

2. Non-written disclosures (Rule 43*bis*.1 and 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CA2004/001503

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted :

Notes to the applicant:

A statement which incorporates by reference any other document may not comply with the regulations of some states. Such statements were observed on page 66.

Unidentified trade-mark may not comply with the regulations of some states. Such unidentified trade-marks were observed on page 65.

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made :

Claim defects

Claims 1-4, 14, 17, 22, 28-31, 34-35 and 39 do not comply with article 6 of the *Patent Cooperation Treaty (PCT)*. The following discrepancies were observed:

- The use of the expression "target epitope" (claim 1, line 18) is a source of ambiguity. It is not clear whether said target epitope is *accessible*, *inaccessible* or *converted*.
- The terms "modifying" (claim 1, line 11) and "modified" (claim 39, line 5) do not lead to the intrinsic and knowledgeable interpretation. The terms "denaturation" and "disaggregation" should be incorporated for clarity, in claims 1 and 39.
- The term "blocking agent" (claims 1, 9, 28-29, 31, 35, and 39) does not lead to the intrinsic and knowledgeable interpretation, and renders the claims vague. This term should be more defined.
- There appears to be few clerical errors, as follow:
  - a space is missing between the terms "aggregate" and "and" (claim 1, line 8);
  - claim 17 should end with a point instead of a comma;
  - there are two claims numbered "28" (page 75);
  - claims 28 (second occurrence) and 29, both have an extra point after the claim number;
  - there is the word "in" missing between the terms "is" and "i)" (claim 39, line 2).
- The term "or" (claim 28, second occurrence, line 4; and claim 30, line 3) is a source of ambiguity. Said term should be replaced with the conjunction "and".
- The full expression of each abbreviation appearing for the first time should be incorporated in the claims, followed by its abbreviation placed in parenthesis. The following abbreviations constitute a source of ambiguity and render the claims unclear :
  - PrP^{Sc} (claim 2, line 4), scrapie (or non-wildtype) isoform of the prion protein;
  - APP (claim 3, line 2), amyloid precursor protein;
  - SOD1 (claim 4, line 1), superoxide dismutase-1;
  - SDS (claim 14, line 1), sodium dodecyl sulphate;
  - BSE (claim 22, line 1), bovine spongiform encephalopathy;
  - CJD (claim 22, line 1), Creutzfeldt-Jacob disease;
  - CSF (claim 30, line 3), cerebro spinal fluid;
  - ELISA (claim 34, line 2), enzyme linked immunosorbent assay.

Description defects

The description encompasses some discrepancies, and thus, do not comply with article 5 of the *Patent Cooperation Treaty (PCT)*.

- The inclusion of internet references does not constitute a permanently retrievable non-patent document. Such internet references should be deleted or replaced with document references, which are clearly identified and permanently available to the public. Internet references were found on pages 5-7.

The figures and the description do not comply with rule 10.2 of the *Regulations Under the PCT*. Reference characters of figure 6, panel B (▲ and ■), are inconsistent with the reference characters disclosed in the description pages 24 and 62-63 (_ and π).

Supplemental Box 1

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of box V (2. Citations and Explanations)

A. Novelty
Claims 1-39 comply with article 33.2 of the *Patent Cooperation Treaty (PCT)*. The above claims are considered novel over the prior art. The proposed conformational-based detection method of a candidate polypeptide appears to be novel. The approach of contacting said polypeptide with a "blocking agent", prior to the steps of denaturation and detection, was not retrieved in any prior art documents.

B. Inventive step
Claims 1-39 lack an inventive step and do not comply with article 33.3 of the *Patent Cooperation Treaty (PCT)*. Although the claims on file appear to be novel, it was found that they lack an inventive step. The subject matter of the above claims would have been obvious to a skilled person, having regard to D1-D3.

The congruence between the subject matter of claim 1 and the subject matter of D1 is illustrated in the table below (Supplemental box 2). It is noted that the alleged invention differs from D1, in that the method of claim 1 suggests a chemical modification (via the use of a "blocking agent") of a target epitope for preventing antibody recognition of said epitope. More precisely, the use of said blocking agent leads to the destruction of epitopes on monomeric proteins (PrPc), but not on aggregated proteins (PrPsc). Accordingly, it seems that this epitope destruction could also be done using proteinase or hydrolase (D1, col. 13, D3).

Although D1 slightly differs from the alleged invention, not suggesting the use of a blocking agent, D2 discloses a method for chemical modification of epitope (D2, page 3671), involving DEP and succinic anhydride. It is thus clear the combination of the prior art documents D1 and D2 would render the subject matter of claim 1 obvious to a skilled person in the art.

The dependent claims 2-30 refer to standard options in the art. For instance, it is well established that:

- prion protein (PrP) comprises two conformations: PrPc and PrPsc (D1-D2);
- DEP and succinic anhydride could be used as chemical modifying agent (blocking agent) (D2);
- polypeptide could be denatured with heat, detergent, or chaotropic agent (D1; and D3, page 8, 1st paragraph);
- known antibodies 6H4 or 3F4 can be used for detection of prion polypeptide epitope (D1-D3);
- non-wildtype protein conformation is associated with numerous disease, namely prion diseases, alzheimer, and parkison (D1-D3).

The kit of claim 31 fails to include the "blocking agent", an essential element since it react with target epitopes to prevent binding with the detecting agent. The absence of said "blocking agent" renders the above claim obvious to a skilled person in art, having regard to common knowledge and standard options in the art. Patentability for kit is assessed independently on the function of the kit. Hence, a kit comprising strictly a detecting agent is already known in the art. Again, the dependent claims 32-38, refers to standard options in the art as described above.

Finally, the independent claim 39, which refers to a method of detecting whether a candidate polypeptide has been modified to convert any accessible target epitope to accessible epitope, also lacks an inventive step. The method of claim 39 refers to the same steps and same elements described in claim 1. Therefore, claim 39 would be considered obvious to a skilled person in the art, for the same reasons described above (claim 1).

C. Industrial applicability

Claims 1-39 have industrial applicability as defined under article 33.4 of the *Patent Cooperation*

Supplemental Box 2

Claim	Alleged invention	Cited document D1
1	A method of detecting whether a candidate polypeptide, including a target epitope, is in i) a wildtype conformation or ii) a non-wildtype conformation, comprising:	An assay method involving a sample suspected of containing a protein in at least two conformations: a disease conformation and a non-disease conformation. [D1, col.3, lines 18-21; claim 8]
	contacting the polypeptide with a blocking agent that selectively blocks accessible target epitope, wherein in the wildtype conformation, the target epitope is accessible and reacts with the blocking agent, and wherein in the non-wildtype conformation, the target epitope is inaccessible because the candidate polypeptide is aggregated and the target epitope can not react with the blocking agent;	The sample is contacted with a compound which completely hydrolysed the non-disease conformation, but not the disease related conformation. [D1, col.3, lines 20-24; col. 13, Hydrolysis Treatment; claim 8]
	removing unreacted blocking agent from contact with the polypeptide;	The hydrolysis is stopped by adding EDTA. [D1, col.14, Hydrolysis Treatment]
	modifying the candidate polypeptide to convert any inaccessible target epitope to accessible target epitope; and	The sample is subjected to denaturation of the disease conformation via chaotropic salts, denaturing agents or hydrostatic temperature. Denatured protein will bind to a wider range of binding partner, since N-terminus epitopes are exposed following such denaturing conditions. [D1, col.3, lines 30-36 and 55-67; col. 13, unfolding Treatment]
	contacting the polypeptide with a detection agent that binds selectively to the target epitope that was converted from inaccessible target epitope to accessible target epitope, wherein binding between detection agent and converted target epitope indicates that the candidate polypeptide was in a non-wildtype conformation and wherein lack of binding between the detection agent and the target epitope indicates that the polypeptide was in a wild type conformation.	After denaturation, the sample is brought into contact with a binding partner which binds the denatured diseased conformation. An example of antibody is 3F4. Since said antibody can bind to both conformations, this is why the non-disease conformation epitopes are removed, using the first step of hydrolysis. The occurrence of binding indicates the presence of the disease related conformation in the sample. [D1, col.3, lines 33-35, col.4, lines 4-15, claim 8]